

VI. CLAIMS

What is claimed is:

1. Use of an engineered NK cell in the manufacture of a medicament for treating a cancer,
5 wherein the engineered NK cell that has been modified to comprise a knockout of the CD38 gene.
2. The use of claim 1, wherein the cancer comprises multiple myeloma, acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL), or Blastic plasmacytoid dendritic cell neoplasm (BPDCN).
- 10 3. The use of claim 1 or 2, wherein the medicament further comprises an anti-cancer agent comprising a small molecule, antibody, peptide, protein, or siRNA that targets CD38.
4. The use of claim 3, wherein the anti-cancer agent comprises Daratumumab, isatuximab, TAK-079, or MOR202.
5. The use of claim 3 or 4, wherein the medicament further comprises an angiogenesis
15 inhibitor and a steroid.
6. The use of claim 5, wherein the angiogenesis inhibitor comprises Pomalidomide, Lenalidomide, or Apremilast.
7. The use of claim 5, wherein the steroid comprises a glucocorticoid.
8. The use of claim 7, wherein the glucocorticoid comprises dexamethasone,
20 betamethasone, prednisolone, methylprednisolone, triamcinolone, or fludrocortisone acetate.
9. Use of an engineered NK cell in the manufacture of a medicament for treating a cancer, wherein the engineered NK cell is obtained by a said method comprising
 - a) obtaining a target NK cell to be modified;
 - b) obtaining gRNA specific for the target DNA sequence;
 - 25 c) introducing via electroporation into the target NK cell, a RNP complex comprising a class 2 CRISPR/Cas endonuclease (Cas9) complexed with a corresponding CRISPR/Cas guide RNA that hybridizes to a target sequence within the genomic DNA of the target NK cell creating an engineered NK cell.
- 30 10. The use of claim 9, wherein the NK cell is a primary NK cell that has been modified ex vivo and after modification transferred to the subject.
11. The use of claim 9, wherein the NK cell is an autologous NK cell.

12. The use of claim 9, wherein the NK cell is from an allogeneic donor source.
13. The use of claim 9, wherein the NK cell is expanded *ex vivo* with irradiated mbIL-21 expressing feeder cells.
14. The use of claim 9, wherein the medicament comprising the engineered NK cell is prepared to be administered separately from administration of IL-21 or irradiated mbIL-21 expressing feeder cells.
15. The use of claim 9, wherein the RNP complex targets the CD38 gene.
16. A genetically modified NK cell comprising a knockout of the gene encoding clustering of differentiation 38 (CD38) made by a comprising:
- 10 a) obtaining a target NK cell to be modified;
- b) obtaining gRNA specific for the target DNA sequence; and
- c) introducing via electroporation into the target NK cell, a RNP complex comprising a class 2 CRISPR/Cas endonuclease (Cas9) complexed with a corresponding CRISPR/Cas guide RNA that hybridizes to a target sequence within the genomic DNA of the target NK cell, thereby creating the genetically modified NK cell.
- 15 17. Use of the genetically modified NK cell of claim 16 in the manufacture of a medicament for treating cancer.
18. The use of claim 17, wherein the medicament further comprises an anti-cancer agent comprising a small molecule, antibody, peptide, protein, or siRNA that targets CD38.
- 20 19. The use of claim 18, wherein the anti-cancer agent comprises an anti-CD38 antibody.
20. The use of claim 19, wherein the anti-CD38 antibody comprises Daratumumab, isatuximab, TAK-079, or MOR202.
21. The use of any of claims 17-20, wherein the cancer comprises multiple myeloma, acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL), or Blastic plasmacytoid dendritic cell neoplasm (BPDCN).
- 25 22. Use the genetically modified NK cell of claim 16 in the manufacture of a medicament for reducing NK cell fratricide in a subject receiving anti-CD38 immunotherapy.

